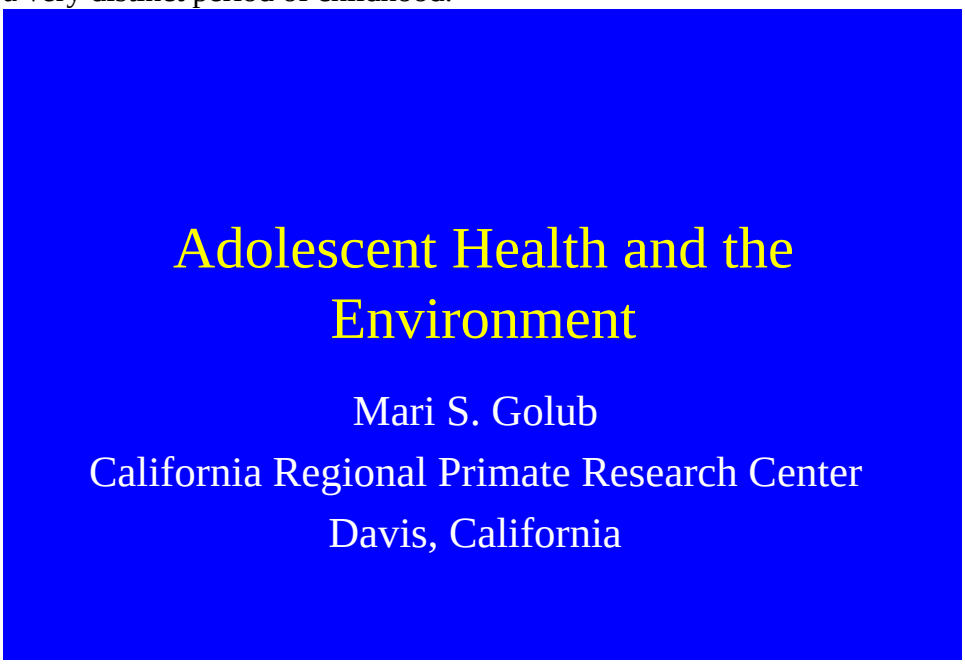
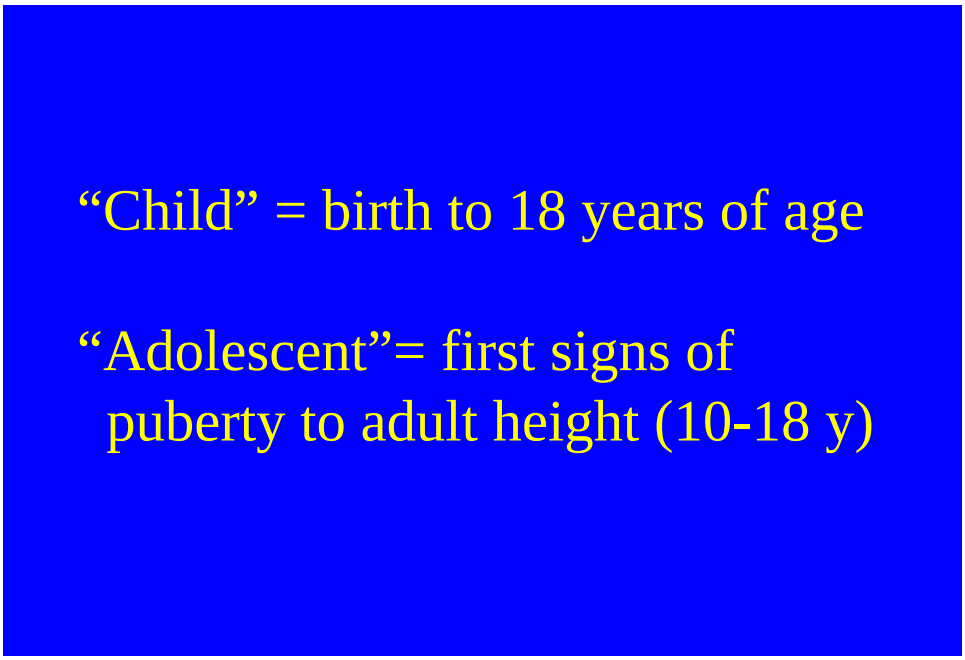
Adolescent Health and the Environment: Dr. Mari Golub

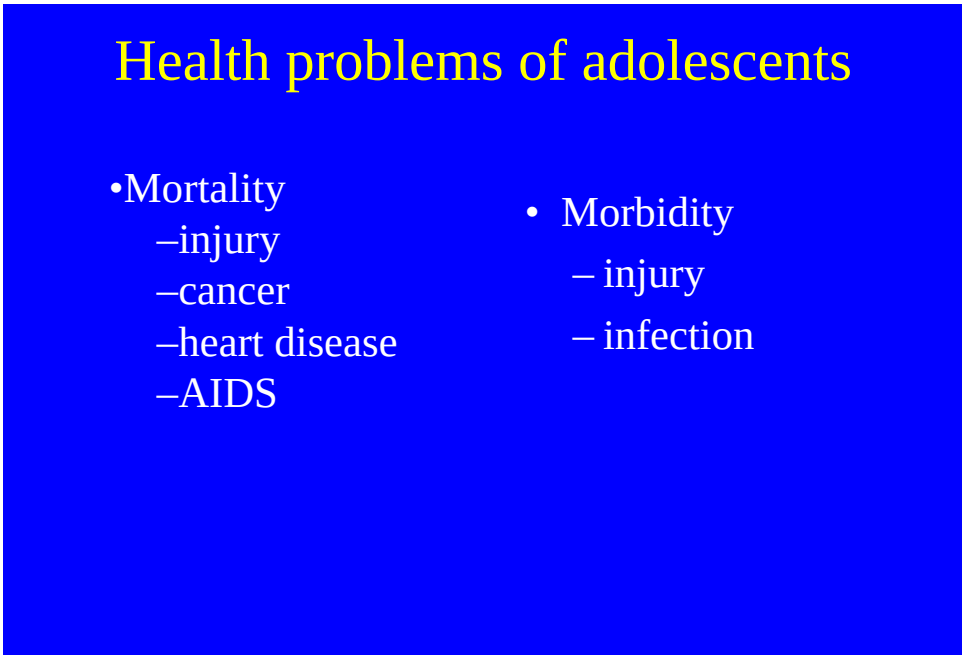
DR. GOLUB: It's great to be here with so many people with whom I've shared so many adventures in risk assessment.
When I became interested in this area it soon became clear that there is no literature on adolescent toxicology, so all I can do today is present a few concepts and a little bit of information.
It is important to realize-and I hope you will at least take away this message -that adolescence is a very distinct period of childhood.



When the U.S. EPA set up its program on child health they identified childhood as extending from birth to 18 years of age. A workable definition of adolescence is the period between the first signs of puberty to the attainment of adult height, approximately 10 to 18 years of age. So basically adolescence is half of childhood.

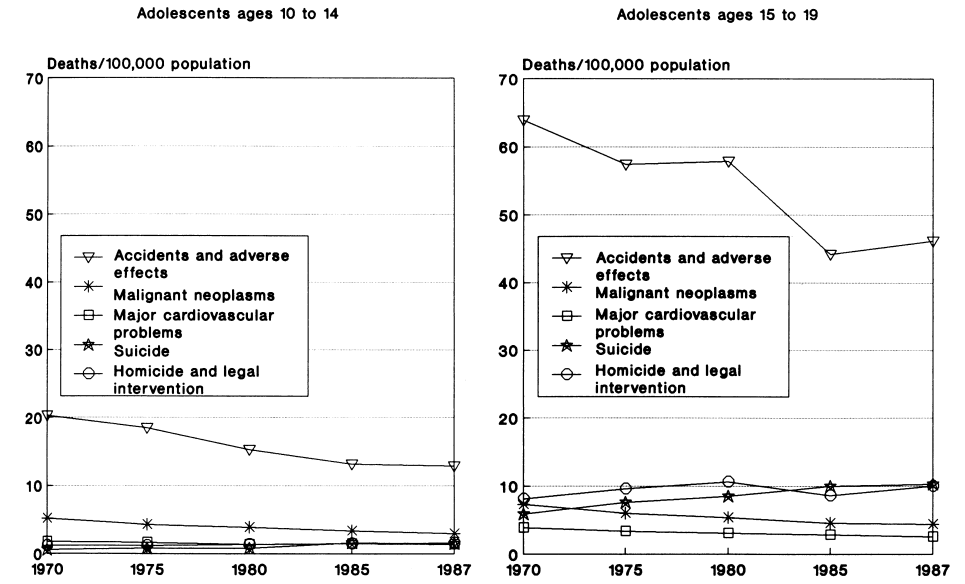
Adolescent Health and the Environment: Dr. Mari Golub





The health problems of adolescents are somewhat unique. Injury tops both mortality and morbidity in terms of incidence. Injury isn't a common end point in toxicology but it's something worth thinking about. It includes accidents, such as auto accidents, sports accidents, homicide, and an interesting category called "legal intervention."
So injury is important to think about: Could toxicants contribute to the incidence of injury in adolescence? Infection is the second leading cause of morbidity in adolescence. It is also important to think about toxicants in connection with the incidence of infection.

Adolescent Health and the Environment: Dr. Mari Golub

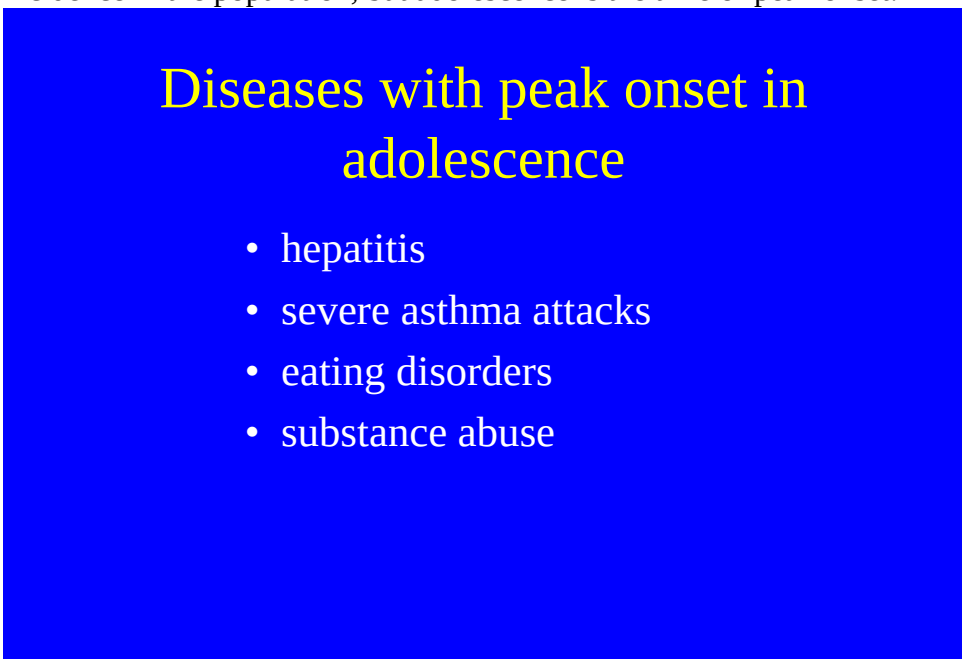


From: OTA, 1991

There are a number of diseases that appear around the time of puberty, and the onset of these diseases could potentially be affected by toxicant exposure.

Schizophrenia first occurs during late adolescence and into the 20s; we don't know when the actual etiological origin is, but this is when it appears. Autoimmune diseases, which have a predominance in women, first appear in late adolescence and into the 20s. Sleep apnea and other sleep disorders first occur during adolescence. The onset of diabetes is much earlier in adolescence, 10 to 13 years old is the peak incidence of onset. Coronary artery disease -- we know that plaque accumulation begins during this time period, and also thyroid disorders appear around the time of puberty. So these are all diseases to think about in terms of toxicant impacts in adolescence.

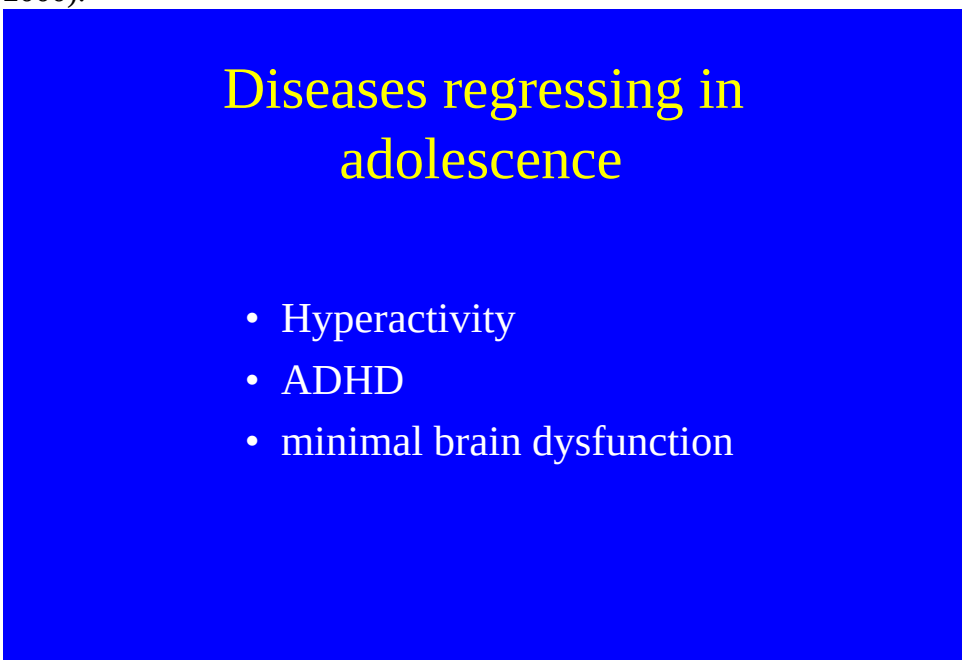
There are also some common diseases whose peak onset time is in adolescence, including hepatitis, an extremely important public health issue, severe life-threatening asthma attacks, eating disorders, bulimia, anorexia nervosa, and substance abuse. There is not necessarily a high incidence in the population, but adolescence is the time of peak onset.



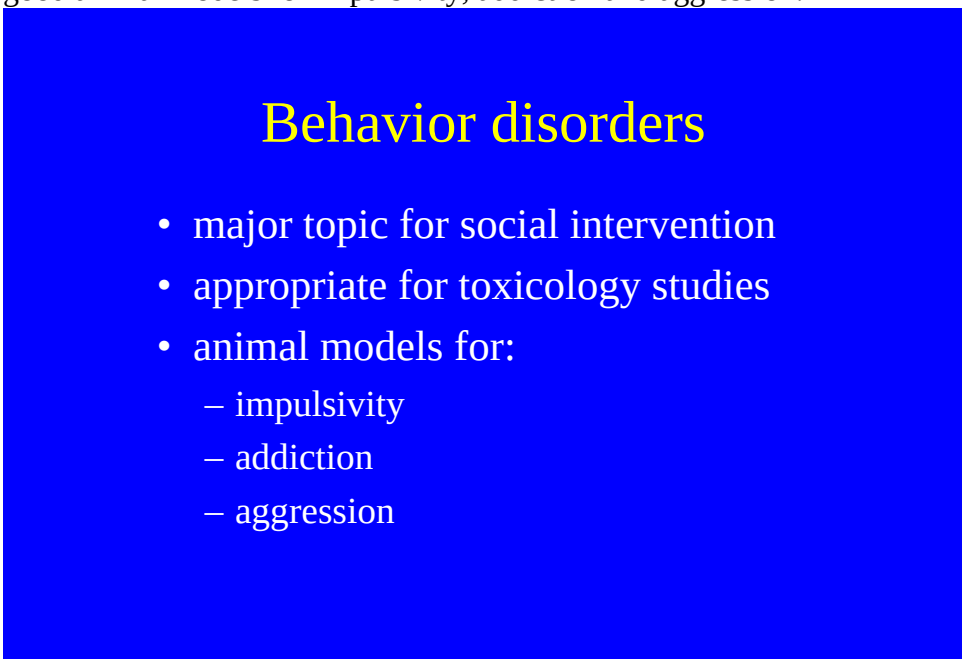
There are also diseases that regress in adolescence; little cluster of CNS syndromes, hyperactivity, ADHD, and minimal brain dysfunction. The normal regression of these diseases in adolescence could possibly be affected by toxicants.

Keep in mind, I'm presenting gross generalizations, and there is extensive literature in each of these areas. There are many more specific ideas on how these things happen and why they happen in adolescence. If you're interested please consult the original literature, much of which

is cited in a recent review article I have published (Environmental Health Perspectives, April 2000).

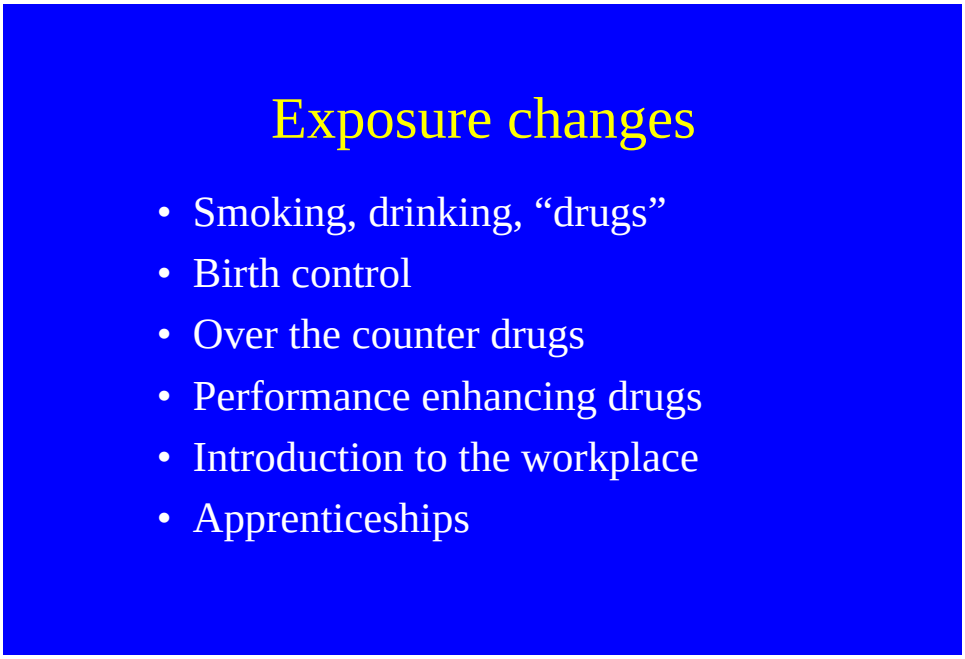


Behavior disorders aren't specifically public health diseases, but they're a very important topic for social intervention and societal concern in adolescents. Are they appropriate endpoints for toxicology studies? I think they could be; some of the behavior disorders such as conduct disorders, risk-taking, aggression and assault are common in adolescents. There are animal models for these behaviors, they could be studied in relation to toxicants. There are particularly good animal models for impulsivity, addiction and aggression.



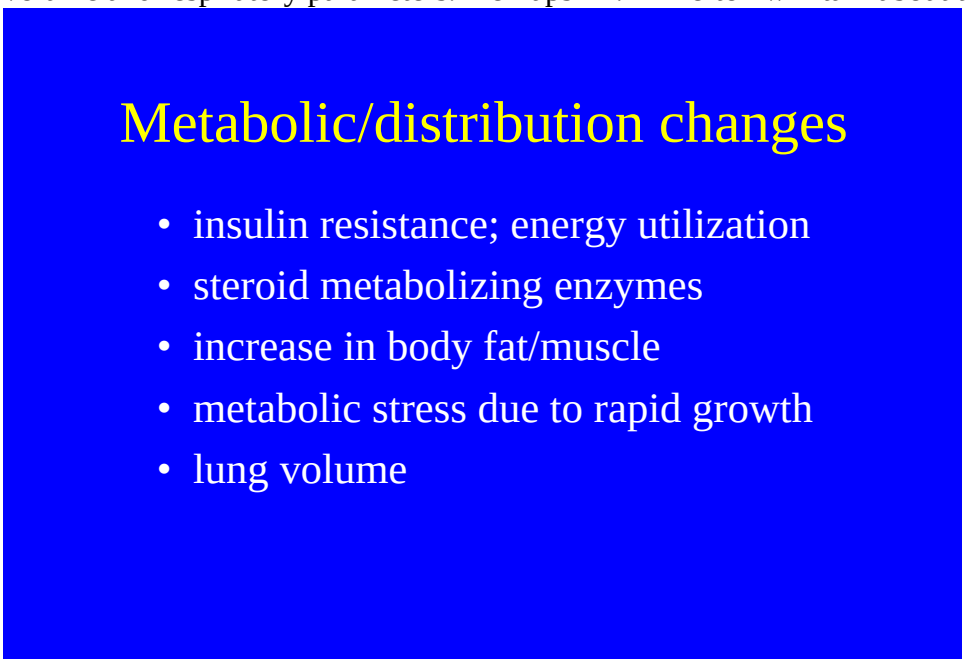
Moving on to a different topic, exposure change in adolescents. I think the first exposure change listed here is one that we're all familiar with, the onset of smoking, drinking, and the use and abuse of illegal drugs. The incidence I think is about 30%, 40% and 50% for eighth-, ninth- and

tenth-graders in terms of ever having used an abused drug. I don't have the statistics on smoking and drinking, but I think they're fairly familiar to all of us.
What does this have to do with toxicants? Well, first of all, in our broader definition of toxicants, all these agents are toxicants--they have toxic effects on the nervous system and other systems. Also their interactions with environmental toxicants are important to think about. Enzyme activation and induction, changes in susceptibility of cells due to accumulation of exposures, and so forth.
Birth control begins in adolescence. Talk about an estrogenic effect, birth control pills will do that for you. I saw recently on the internet that the FDA is thinking about converting many birth control regimens to over-the-counter drugs, which will make them even more accessible to adolescents during this period when their tissues are maturing under the influence of estrogen.
Performance-enhancing drugs. Recent statistics show that about 3% of teenagers take performance-enhancing drugs, such as anabolic steroids and stimulants.
And then of course, most important, the introduction to the work place. Most teenagers begin to work during this time. As you know, we do not have any protective work place standards that are specific to children. Certainly this is a regulatory area that could use some involvement of the child health programs. Even 12 and 13 year-olds work -- recent statistics show that 30 to 35% of children in this age group work. They may not be employed, but they are in the workplace in one capacity or another --helping families, part-time jobs, getting a little money on the side informally.
Also there are apprenticeships that occur during this time -- helping your dad fix the car, 4-H clubs, other things, other places where there'll be intense exposures to chemicals with perhaps not much instruction. I've had an opportunity to talk to the
4-H program people and there’s not much awareness of possible damage to teenagers in 4-H programs from pesticide use.



There are wonderful pharmacokinetics going on during this period but not too much is known quantitatively. Insulin resistance is typical of adolescence, particularly early adolescence. It's in connection with changes in energy utilization that are required by the rapid growth and high

muscular activity in this age group. The steroid metabolizing enzymes in the liver kick in, in connection with the greater production of steroid hormones, and this is important to toxicant metabolism. There is an increase in body fat and body muscle, which will influence actions of toxicants that partition into those compartments.
There can be considerable nutritional stress due to rapid growth. Toxicants that can influence nutrient deficiencies are particularly active at this time. I first became interested in this area through my studies of zinc deficiency in adolescence. And then there are changes in lung volume and respiratory parameters. Perhaps Dr. Pinkerton will talk about this a little more later.



There are very distinct maturational events that occur in adolescence. Morphological changes like neural tube closure are the basis of toxicant induced teratogenesis and similar dramatic morphological changes in adolescence could be disrupted by toxicants.
Here are some of those events--the growth spurt, puberty, thymic involution, the completion of mineralization at the end of the long bones and epiphyseal closure, which leads to the cessation of linear growth.
I added these last three “events” (braces, the prom and the SAT), to remind you that the teenage trials and tribulations that we think of as psychological and social have their basis in biological events in the adolescent period. There are reasons why people have braces when they're adolescents, it isn't just to humiliate and embarrass them, it’s when formation of the jaw is completed. Why do we do intelligence testing in adolescence? Why are the social, the heterosexual interactions so very distressing to people during this time period? The underlying biology is important and can be influenced by exposure to toxicants.

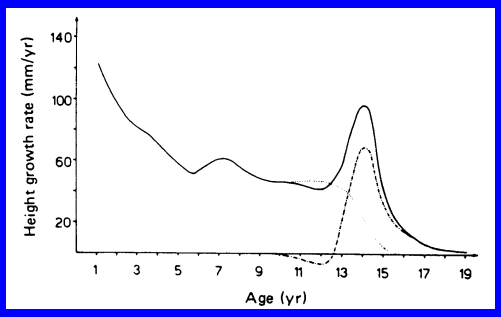
Adolescent events

- The growth spurt
- Puberty
- Thymic involution
- Epiphyseal closure
- braces, SAT, the prom

The growth spurt has a lot to be said about it, but I just want to make one point, and that has to do with species differences.
The human growth spurt is a very distinctive characteristic, and many people think it's unique to primates. There is a decrease in the velocity of growth beginning in childhood right up to the time of early puberty, then an increase, and then again a dramatic decrease, a discontinuous pattern. Whereas, in rodents, a common laboratory animal in toxicology experiments, there's more of a continuous decrease in the growth rate during this time period. To study the growth spurt, the current animal toxicology models such as rats and mice aren't really as appropriate as they might be.

The Growth Spurt: Species differences in pre-adult growth

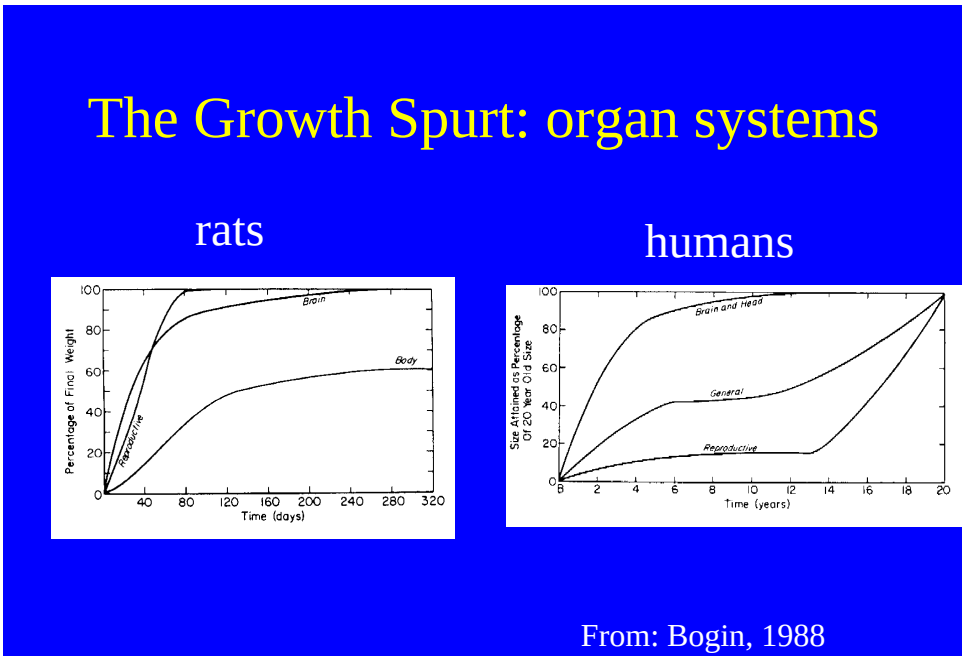
- Continuous
- Discontinous



From: Bogin, 1988

The growth spurt has an internal component. These slides show different systems, cardiovascular, respiratory, etc.

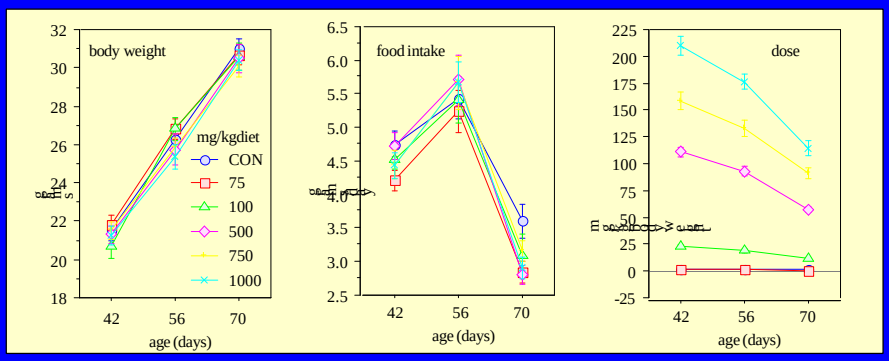
Adolescent Health and the Environment: Dr. Mari Golub



I'd like to make the point that body growth does not cease at the end of adolescence in rats and mice. Only 60% of the body weight is reached by the end of the first year of life in rodents (about half their life span), they still have a long way to grow, whereas, by 20 years of age adult height is pretty much attained in humans. That's because of a lack of epiphyseal closure in rodents.

Also the reproductive system and the central nervous system mature at a similar rate in rats, and they reach their adult size at about the end of puberty, whereas, in humans the brain weight -- and this is just in terms of size -- is 100% that of an adult prior to the beginning of puberty, but the reproductive tract is lagging behind and does most of its growth during the adolescent period. So the growth of the different organs is very much dependent on species, as well as on developmental stage.

Changes in administered dose



Male Swiss Webster mice

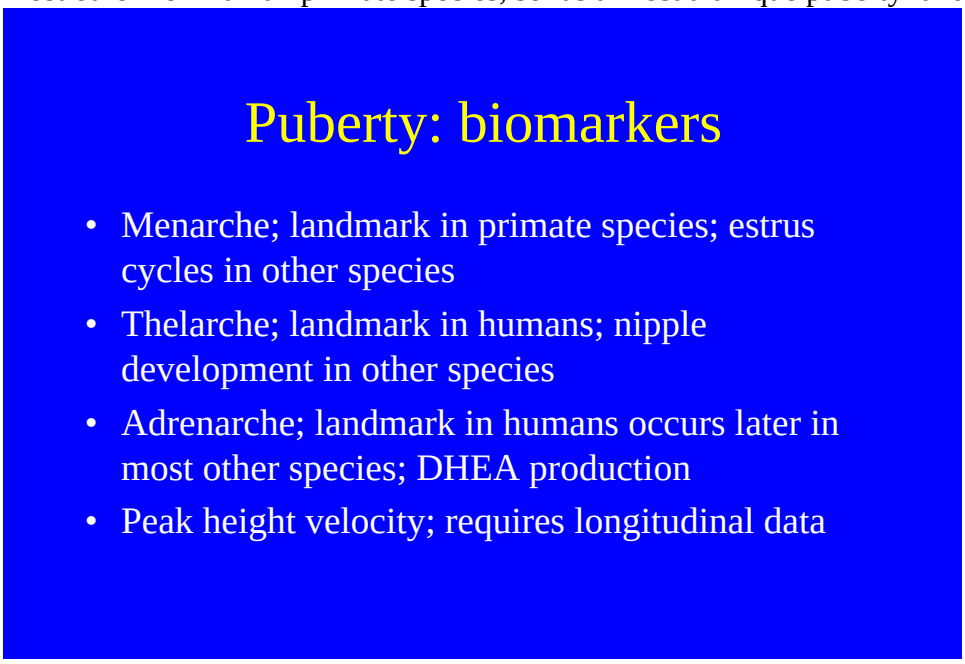
Puberty is the most important landmark of adolescence. How do you measure puberty in humans? There is a method for doing this, the Tanner stages. I wanted to mention it because you might not be familiar with it, it's been used since the '50s or '60s in clinical practice, and it's also used in clinical studies. It's a way of rating the stage of pubertal development. There are five stages in each category, penis or breast development and pubic hair development. The stages are standardized by comparison with photos and there are also text descriptions.

Puberty:biomarkers in humans. The Tanner stages

- Penis/Breast development, pubic hair
- 5 stages for each category
- standardized by comparison with photos
- extensive normative data
- well established correlations with other pubertal markers

There is extensive normative data on this parameter. If you were able to use this parameter in an epidemiology study on toxicology of adolescents this would be the way to go. It does require, of course, a physical examination. *(see Dr. Rogan's talk for further comments).* And there are well established correlations with other pubertal markers. So, there is a way to quantify and measure puberty in humans.

There are also discrete markers of puberty in humans, such as menarche. This is a landmark in primate species. Estrous cycles would be the landmark in common laboratory species we use in toxicology.
Thelarche or breast development is also a landmark in primate species, and would correspond to nipple development in rodents.
And adrenarche, or the beginning of the production of steroid hormones in the adrenal glands occurs in humans around the time of puberty, but much later in most other species including most other non-human primate species, so it's almost a unique puberty landmark for humans.



I think we're all going to become more familiar with the landmarks of puberty in rodents since they're now included in the standard reproductive toxicology protocols of FIFRA and U.S. EPA. The vaginal opening is the landmark for females and preputial separation for males. Basically this just involves the cornification and disappearance of the epithelial layer over the vaginal opening and at the tip of the penis. These landmarks are easy to identify. These processes by which these membranes become cornified and disappear may have nothing to do with the puberty landmarks of humans, so we need to have some sort of a validation of how well we can use them to generalize to onset of puberty in humans.
Ano-genital distance is currently an important end point in animal studies. It corresponds to the other aspects of reproductive tract maturation in rodents, but it's not discrete. So, we don't know what a mature ano-genital distance is. And it's a very valuable marker, but a lot of things have to be taken into consideration for its quantitative use as an index of reproductive tract maturation such as onset of estrous cycles and completion of the first sperm cycle.

Puberty: Rodent biomarkers

- vaginal opening
- preputial separation
- anogenital distance
- onset of estrus cycles
- completion of first sperm cycle
- no epiphyseal closure

This slide shows data on the occurrence of preputial separation and vaginal opening. I think some people may be surprised to find out that rats and mice aren't mature at the time of weaning. There's a period of at least three or four weeks that would correspond roughly to adolescence after weaning when the reproductive tract matures. So 33 days and 43 days in rats are the ages for puberty in females and males respectively using these landmarks, a little bit earlier in mice.

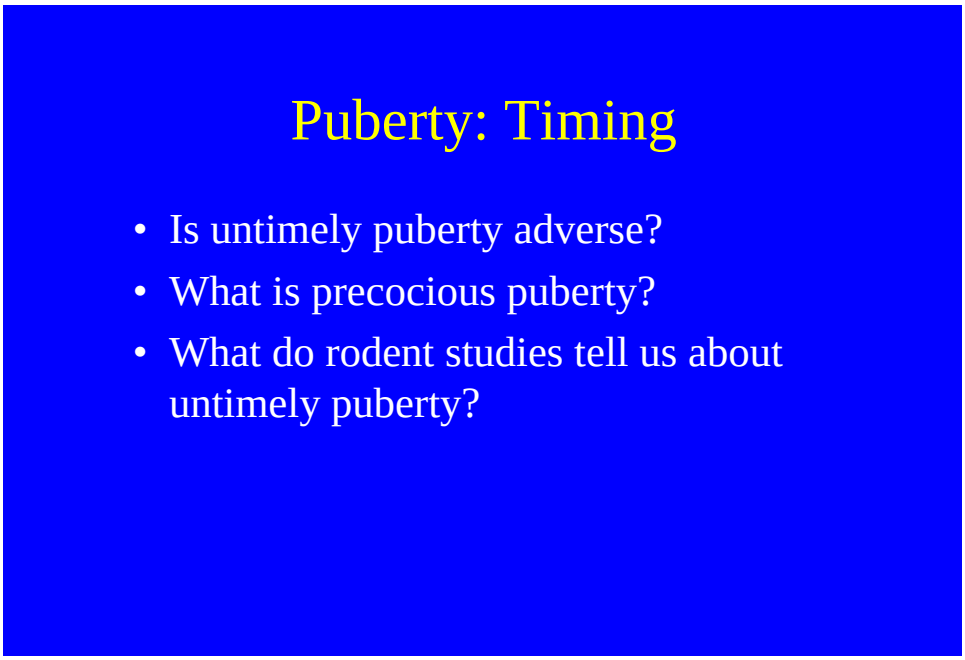
Puberty: landmarks in rats

	Mean age (days)	*SD*	*# of Studies*	*Range*
Preputial separation	43.6	0.95	38	41.8-45.9
Vaginal opening	33.4	0.77	33	31.6-35.1

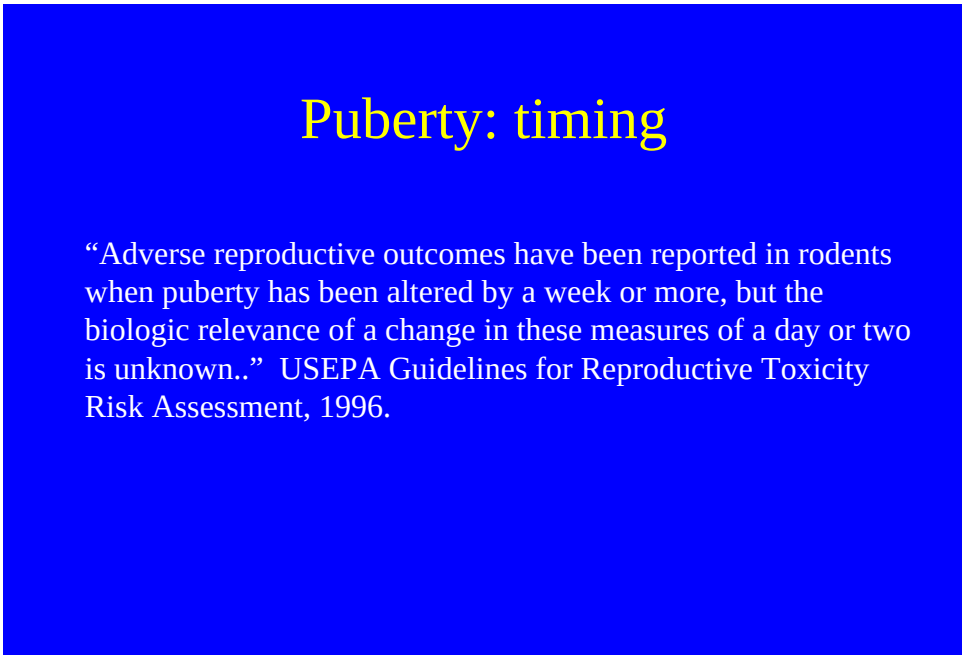
From: Clark, 1998

Is there a problem when puberty is early or late, either in standard reproductive tox screening or in humans, does it matter if puberty is early or late? Is early or late puberty onset considered adverse, or a sign of toxicity? I want to spend just a little bit of time on that because it's probably the risk assessment marker we'll most be dealing with in terms of adolescence and puberty.

Adolescent Health and the Environment: Dr. Mari Golub



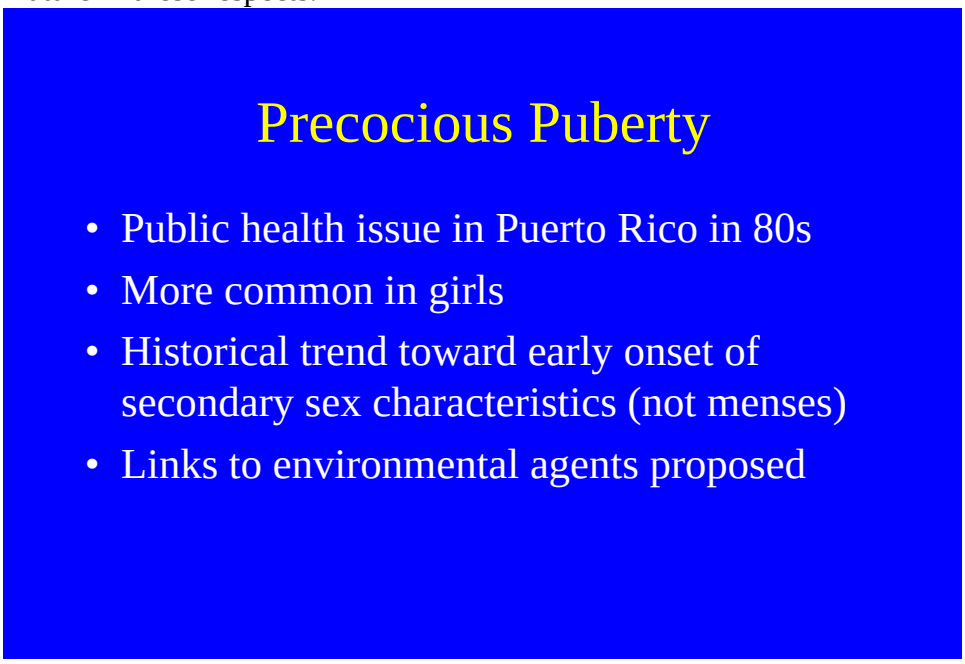
This statement from the U.S. EPA guidelines outlines a position on when alterations in the age at puberty can be considered adverse. Their advice is that adverse reproductive outcomes have been reported in rodents when puberty has been altered by a week or more, but the biological relevance of a change of these measures of a day or two is unknown. This is important because you can get statistical differences of less than a day and we need to know how to interpret that for risk assessment.



Precocious puberty, however, is a diagnosis that's important in human clinical situations. It was a public health issue in Puerto Rico in the late '80s, more common in girls, and it was linked to environmental agent exposures, although this was never firmly established. It's still being investigated, so we don't know if environmental agents can cause precocious puberty.

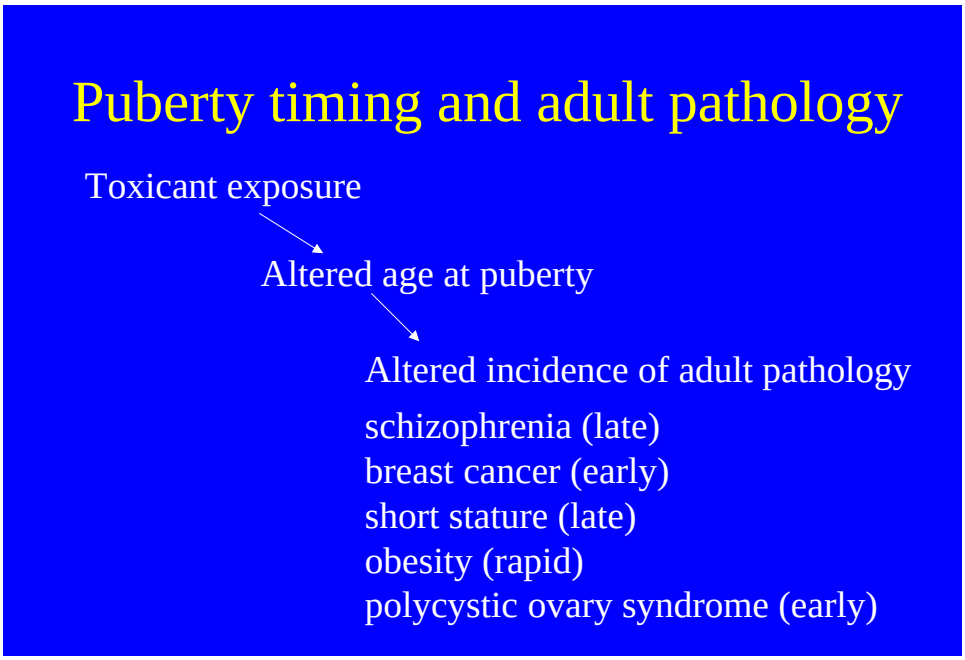
Adolescent Health and the Environment: Dr. Mari Golub

In precocious puberty there's a complete pubertal development including reproductive tract maturation and epiphyseal closure, so that children at the age of five through maybe seven are mature in these respects.

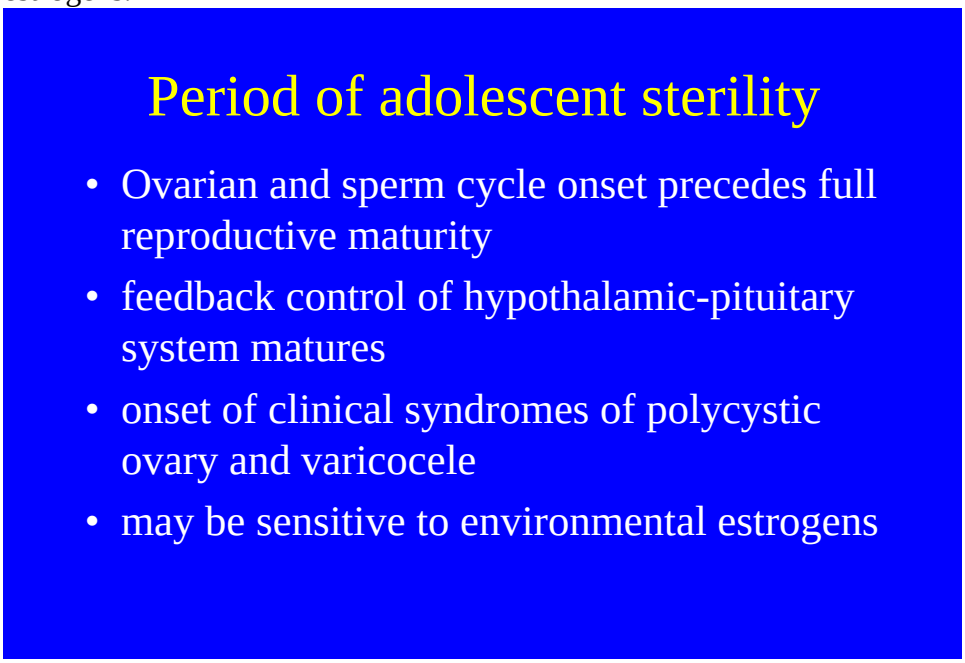


There is a historical trend toward the earlier onset of secondary sex characteristics, but I wanted to make the point that actual puberty is pretty stable as far as the age of its appearance, at least during the time when we have good statistics. Based on this information I don't think it would be a valid point to conclude that there has been a trend toward earlier puberty due to exposure to environmental chemicals.

However, there is an issue of puberty timing in respect to adult pathology because clinical studies have shown that altered age at puberty is associated with altered incidence of adult pathologies. For example, schizophrenia is associated with late puberty, breast cancer with early puberty, short stature with late puberty, obesity with rapid development during puberty, and polycystic ovary syndrome with earlier puberty. It's possible that the timing of puberty could be important. It’s something that we need to know more about so that we can take it into account in risk assessment.



There is a period immediately after puberty that I think is very important from the viewpoint of the impact of environmental estrogens, and that's a period of so-called adolescent sterility. It occurs after menses and the first sperm cycle, but before there's full reproductive ability. During this time the very elaborate systems that control feedback of the gonadal hormones within the hypothalamus and the pituitary are being established and could be susceptible to exogenous agents. It's a time of onset of polycystic ovary and varicocele, two child health reproductive problems, and I think it could potentially be influenced and disrupted by environmental estrogens.



This is just a slide with some data demonstrating the gradual onset of reproductive function after puberty. This is the month after menarche and the percent of 13 to 16 year old girls that have ovulated. So during the first year and a half after menses only 32% of the girls had ovulated, and

in the next 10 or 11 months it's up to 46%, and 31 months, nearly three years after menarche some 40% of the girls had not yet ovulated.

Gradual establishment of ovulatory cycles in 13-16 year olds

Months after Menarche	% ovulated
0-18	32
19-30	46
≥31	61

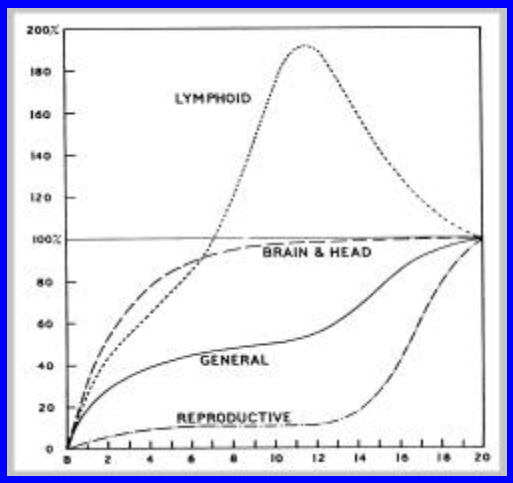
From:Talbert et al. 1985

I wanted to mention thymic involution, it's not something that we think about a whole lot because there are no external visual markers but it is characteristic of the adolescent period. It's not so much the thymic involution that's important but the connection with the dispersal of the responsibility for processing T-cells away from the thymus and into the mucosal system.
It's during this time that mucosal immunity really is accelerated, in the gut as well as the reproductive tract, obviously a great need during this time when sexual activity begins. Thymic involution is a good landmark, a quantitative landmark, but it cannot be assessed noninvasively. In the periphery and in human populations there are changes in the T-cell population ratios that can be detected by *FACS* in order to study this phenomenon.
And this slide shows that the lymphoid system has a very distinct developmental pathway. It increases during the time of adolescence, peaks right around 12 years of age, but then it decreases, and this is the thymic involution and the change in the processing of T-cells around that time. So it could be a time when immunotoxicants could disrupt the maturational process.

Thymic involution

- Corresponds to development of mucosal immunity
- processing of T-cells in gut and reproductive tract
- change in T-cell populations in peripheral blood samples by FACS

Thymic involution

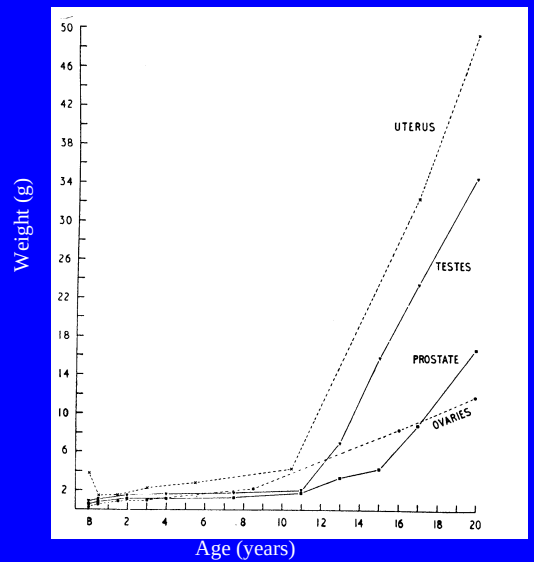


Reproductive organ changes. I just wanted to mention that in addition to the growth of reproductive organs, which we can't see as well as secondary sex characteristics, there are qualitative changes. These include the development of the male accessory organs for ejaculation, changes in the composition and thickness of the vaginal epithelium, the establishment of the uterine cavity and secretory activity, and the change in orientation of the uterus. So these are changes that could reach the level of a malformation if they were interrupted by exogenous agents.

Reproductive organ changes

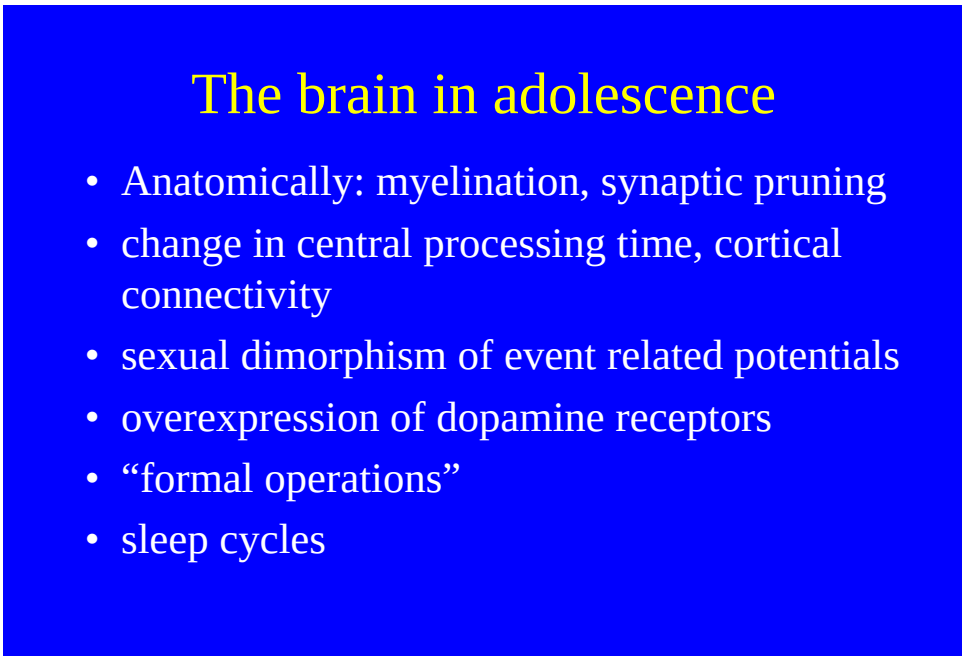
- Onset of spermatogenesis
- development of the male accessory organs
- vaginal epithelial thickness, pH and glycogen content
- establishment of the uterine cavity and secretory activity
- change in orientation of the uterus

Rate of reproductive organ growth



I'd like to close, but not without mentioning my favorite organ system, the brain. Obviously very important in adolescence, and more work has been done than you might imagine.

Adolescent Health and the Environment: Dr. Mari Golub

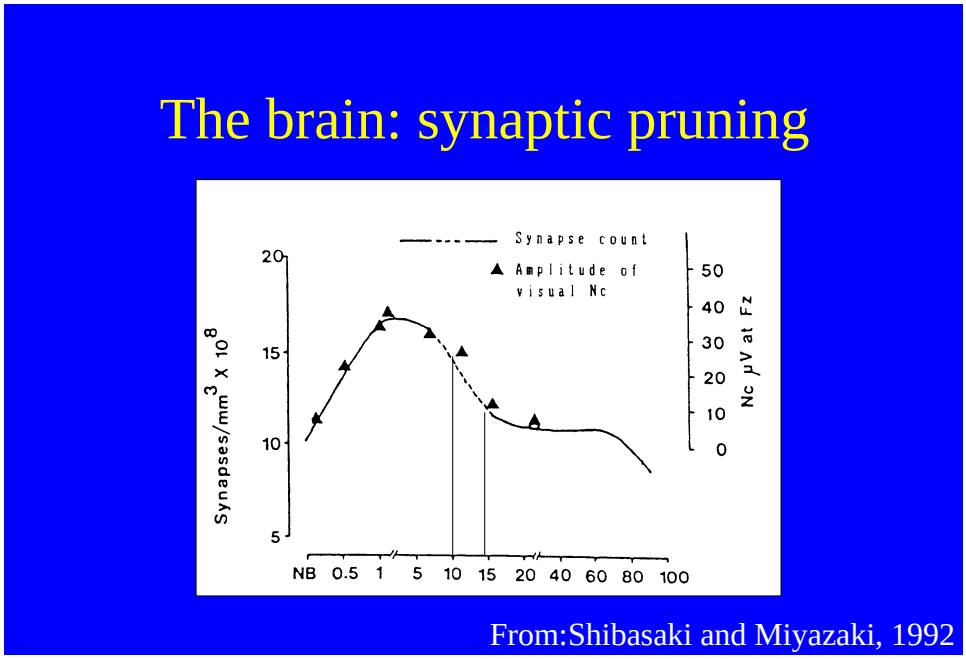


Anatomically two concepts are important: myelination and synaptic pruning. Both of these changes lead to changes in central processing time and cortical connectivity. It's the cortical pathways between the two sides of the brain and up and down between the forebrain and the midbrain that become myelinated in the last stages of adolescence. And there also begins to be sexual dimorphism of brain function, perhaps most clearly seen and standardized in the event-related potential, an electrophysiological measure. There's an over-expression of dopamine receptors that's been very carefully documented in rats and mice and has also been seen in more recent scanning studies in humans.

There's an onset of formal operations, the last stage of cognitive development that involves the ability to manipulate symbols and concepts. And there's an enormous change in sleep cycles, later bedtimes and later rising times, the “sleeping-in“ phenomenon. That's biology, it really isn't laziness, and it has to do with the fact that much of the hormonal change that takes place during adolescence takes place at night, and these events have to be very closely coordinated with sleep. So if you look at the diurnal patterns of hormone production during adolescence they peak a couple hours after the onset of sleep, and in order for that to happen at the right time you have to go to bed fairly late.

I have been involved a little bit in a nationwide movement to increase the start time of high school because there seems to be a biological basis for feeling that teenagers should not have to get up at seven o'clock in the morning and be alert by 7:30. It's not natural for their age group. So this is an important change that happens during this time. Would it be abnormal for a teenager to go to bed every night at 9:30? Could this be a sign of an adverse effect of a toxicant? This type of a scenario bears consideration.

Adolescent Health and the Environment: Dr. Mari Golub



This diagram is just to show you synaptic pruning. We know that the synapses, the connections between neurons, increase in number during early development, peaking at about one year of age and then declining. But the period from 10 to 15 years of age is the period of most rapid loss of synapses during brain development. So it could be critical to have the processes working correctly that eliminate the right synapses at this time because of the importance of the brain for later successful adult functioning.

Before closing I'd like to thank Laurie Montserrat and Rebekah Torres for their help with the illustrations.

Adolescent Health and the Environment: Dr. Mari Golub

Panel Discussion

DR. DONALD: If there are any specific questions for Mari we'll take those first, then open the floor for general questions for discussion.

DR. MORRY: Dave Morry, OEHHA. Mari, it strikes me that a lot of these changes in adolescence are things that are carried over into adulthood, particularly behavioral things like attention deficit disorder, some of the sexual behavior characteristics, sleep patterns, something that adults differ in tremendously. People who are early risers and people who prefer to stay up late. But I think a lot of these patterns are established during adolescence and then carried into adulthood.

Is there much of an effort to study to what extent these behavioral changes that are established in adolescence are carried into adulthood? And, to what extent do these parameters affect a person for the rest of their life in terms of their behavior?

DR. GOLUB: I think for me a key concept is that adolescence is the time of emergence of a lot of genetic determinants of behavior. For example, adopted children resemble their adopted parents much more closely in I.Q. during the early years, and then when they reach adolescence their I.Q. reverts to resemble that of their biological parents.

So I think what's happening is that the genetic expression during adolescence is coming forth and you could interfere with that. I don't think it's so much a question of there's a pattern established that continues into adulthood, but that there's an underlying pattern that's coming forth that could be either interfered with or promoted perhaps by environmental events.

DR. HOOPER: Kim Hooper, Hazardous Materials Lab.

Nutrition I was curious about. It certainly has an effect on age at onset of menses. For other aspects of sexual maturation, does nutritional status affect that?

DR. GOLUB: Nutritional status affects the quality and the rapidity,

(here I'm making a very gross generalization) but not so much its occurrence.

I first became interested in this because I've been studying zinc deficiency for a number of years. There is a syndrome in the Middle East where army recruits were coming in at 18 years old, not sexually mature, and zinc deficient. So we studied zinc deficiency in sexual maturation and we weren't able to replicate this relationship in an animal model. It must have been a more complex phenomenon than just the zinc deficiency.

So, I have never seen an arrest of maturation due to poor nutrition. However, you know the studies they're doing now with food restriction, limiting food to 80% or 70% of what the animal would normally eat. I saw one very interesting study where I think it was 55% food restriction, and these animals were becoming mature at something like 110 days of age, maybe three times the age of normal animals. But when they became sexually mature they had normal sexual function, so it was the rate rather than the ability to mature that was affected.

DR. CARLSON: Joy Carlson. I really want to commend you for getting into this, this has been an area of concern for me for a number of years and not many people are addressing it, so bravo. My question has to do with the brain. You mentioned a variety of aspects in the adolescent brain that are different from that of the child and that of the adult, and one of them was the cortical

pathways and the pathways that began to be connecting different parts of the brain in different ways.
It's my understanding -- I'm not a pediatrician, but it's my understanding from some colleagues of mine that there's not a corollary in the animal world to the adolescent brain in the human. If that's the case -- or certain aspects, not totally but certain aspects -- if that's the case how do you think we should proceed in terms of research?

DR. GOLUB: Well, we're currently doing studies of adolescence in non-human primates and all our studies include brain measures. Nonhuman primates provide a much more satisfactory model of human adolescence than rodents.
But I think the problem with rodents is that the front part of the brain, this big thing that sticks up over our eyes in humans and doesn't appear in other animals, is the last part to mature and it's also the last to evolve. So those two things together are what's creating this problem. There certainly is a maturation of intercortical connection in rodents, but the areas and the time and elaboration of that is the striking difference in primates and in rodents.

DR. DONALD: Are there any general questions for Mari or Elaine?

DR. MARTY: This might be to either or both. I read with interest a paper looking at the association of cigarette smoking and breast cancer, and in particular when you started to smoke and the rates of breast cancer. It appeared, at least from this one paper and there may be more now, that it was almost more important when you started to smoke, before the age of 16, and the influence of that on the incidence of breast cancer than how much you smoked.
I'm wondering if there are other environmental toxicants that you are aware of where you can see that exposure at puberty is critical to influencing the rates of breast cancer.

DR. GOLUB: There's quite a bit of information on exposure to estrogen and the incidence of breast cancer and other reproductive problems. There are studies of Turner's syndromes, these are girls who have hypoestrogen production of the ovaries and they're given estrogen during puberty to promote normal reproductive maturation. They do develop a higher level of reproductive tract cancer. There's also a lot of information on estrogen and breast cancer with adolescent exposures.
And I don't know, there's a researcher, Anisomov, who is published in animal literature suggesting that the rapid rate of cell proliferation and differentiation during adolescence predisposes the adolescent to susceptibility to genotoxicants.
So it makes a lot of sense, and there are statistics in small areas but not the kind that you might like to see in order to make a general case.

DR. FAUSTMAN: Yeah, for other agents not during puberty, the idea of the transplacental carcinogens and brain cancers were very time-dependent on when you administered the compounds. And it wasn't just related to metabolism onset or offset. So, it was associated more with proliferation and differentiation status.

DR. DONALD: Okay. I'll pose one final question. Elaine has already addressed this to some extent, but if you've got anything more to say on it please join in. I'll address it initially to Mari.

Adolescent Health and the Environment: Dr. Mari Golub

Given that our current regulatory testing protocols really don't address adolescence what would your suggestions or recommendations be for how we might modify existing protocols or develop new protocols in the future to address that?

DR. GOLUB: Well, that's a good point. It's very frustrating to read studies where dosing begins at 21 days of age and the animal's taken to be an adult. So I think that to me it would be very satisfying if we would begin exposing animals as adults when they are adults, and not when they're 21 or 30 days of age. I think 50 days of age would be the very earliest time that's appropriate to begin "adult" exposure. If the testing protocols would accurately define the adult period they would de facto define the adolescent period.
Similarly, there are very few exposures in rodent studies exclusively in adolescence. They may go from conception to puberty, or they may start at 20 days of age and go to 90 days of age. They never start and stop right in the adolescent period, say 20 to 80 days of age. None of these studies tell you anything specifically about adolescence. It would be necessary to design studies around that age period to really come to an understanding of it.
For humans it would be great if we had exposure data that was specific to adolescents, if that period was delineated in exposure studies instead of having infants, children and adults. And also in terms of human studies adolescent populations could be separated from mature populations in reproductive studies. For example, pregnancies in adolescents could be separated from pregnancies in adults so that we could see unique effects in these susceptible populations rather than lumping them in with adults, which could also distort the adult incidence data.

DR. FAUSTMAN: I was going to make just one comment. We recently were reviewing some of the old lead literature and, you know, lead is something that one might argue overly-studied. But even from the standpoint of impacts on spermatogenesis there are critical differences exactly when you start the exposures in male rates, whether they're just prepubital or at the time of puberty or just after in terms of susceptibility, it can range more than tenfold.
So even with a compound that we think we have a robust data set for, going back and looking at that it's pretty amazing how important this timing of exposure is. So this idea of sorting that out and pulling that out separately for assessment I think is critical.

DR. MARTY: This is for Elaine. It was really intriguing to me to start realizing how complicated it is to study developmental effects. I mean, it's an area where I haven't really done much reading at all.
Have you got a suggestion -- it seems to me you've got the temporal pattern, the windows of susceptibility, overlain on top of that is the dose response, overlain on top of that is the pharmacokinetics. Do you have particular suggestions for areas that really stick out like a sore thumb as not getting enough attention? Or is that all going to be in this book that's coming out?

DR. FAUSTMAN: Well, we'd like to think some things are in there, but I can speak sort of for my own areas.
How do we want to do that? I mean, I think it goes back to my response to one of the earlier questions. It was the idea that I think we need to be more cognizant and start to lump agents together more effectively from what we do know. I hope I didn't just agonize about what we don't know, but start to challenge us as to how we start to lump things together and start to see these commonalities. Because usually rather than a splitter I'm a lumper.

I actually think that we should put together some compounds and set up hypotheses and then enjoy the data when it comes in to disprove that hypothesis about how we've lumped things. To lump them we have to overcome a hurdle that's unbelievably high and that's going to be very difficult to attain. So I would think that if I was in a regulatory context I would start to do some lumping and put it together so that it's in a format that could be testable. At least put it into a format that allows one to do that.
So I don't know, maybe that's too obtuse. I mean, we use the example of proliferative agents. What more obvious lumping would you have for development than to lump those together and then suggest appropriate safety factors or uncertainty, whatever you want to call them, fudging factors. Then let the data challenge that, but make sure that the data comes in.
I think we're kind of apologizing about putting these modifying factors there and not putting it into a context that the data can then argue yes or no to.
And the other thing is to get over the idea of this reluctance to look at sensitive end points because we're scared we don't know what to do with it. It just makes me so irritated. It's like putting ostriches out there. These subtle effects will become more and more subtle, and we shouldn't be scared of them, we should start to look at them on the continuum.

DR. MARTY: Certainly elephant in the living room at this point?

DR. FAUSTMAN: Yeah. I mean, maybe we were justified 20 years ago in not trying to emphasize severity issues in how we do risk assessment. But, we're forced to do that; we have to start to look at that. And rather than being uncomfortable with it, let's start to look at it in terms of what we know.
So, those two things I think are things that we need to really consider.

FEMALE VOICE: I have one more, more of a comment than a question. I think both of you have done an excellent job in bringing out, as Melanie said, the complexity in looking at some of these issues.
But the one complexity that you didn't really address, and maybe somebody in these two days will address, is the outcomes themselves. When you talk about ADHD, Mari had minimal brain dysfunction, which is what they called it when I was in medical school. We have a lot of things, autism, pervasive developmental disorders, Asperger's, all these things. I've heard someone comment that Asperger's syndrome, which is one of the pervasive developmental disorders, might be most of the computer programmers in our society. But all of these have very tenuous case definitions.
And then even intelligence itself, you know, we define intelligence in this culture with a very strongly-verbal component. Whereas, Howard Gardner and others have pointed out, there're a lot of different dimensions to intelligence.
The outcomes themselves vary not only between humans and some of these other species, as has been pointed out. But also we have a lot of problem with case definition, with cultural, social aspects of the whole concept of the outcomes that we're looking at.

DR. FAUSTMAN: That might be a case where -- again, I'm not a behaviorist, but the idea of lumping is not so good. I mean, they never would have found autism and the conditions related to thalidomide if they had been lumpers. So, in fact that was the problem there. So, that's a good example of where you don't want to lump.

DR. GOLUB: I think this is an example of something you don't want to be afraid of either. If it's a real health problem and it really is influencing the lives of people, even if it's difficult and confusing it should be dealt with.

DR. DONALD: Thank you very much.